

BREAST CANCER SCREENING IN THE WORKPLACE : A VIABLE COST-
EFFECTIVE APPROACH TO SAVE LIVES

By

Alica Rucekova

MS in Biology, Florida Atlantic University, 2000

M.D., Comenius University School of Medicine, Slovakia, 1996

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This thesis was presented

By

Alica Rucekova

It was defended on

June 11th, 2008

and approved by

Thesis Advisor:

Joseph Schwerha, MD, MPH

Professor

Department of Environmental and Occupational Health
Graduate School of Public Health
University of Pittsburgh

Committee Member

Evelyn Talbot, DrPH, MPH,

Professor of Epidemiology

Professor of Communication Science and Disorders

Department of Epidemiology
Graduate School of Public Health
University of Pittsburgh

Committee Member:

Nancy B. Sussman PhD, MS

Assistant Professor

Department of Environmental and Occupational Health
Graduate School of Public Health
University of Pittsburgh

Joseph Schwerha, MD, MPH

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Abstract

Background: Breast cancer is a worldwide public health concern. Breast cancer now ranks first not only in the industrialized world but also in the developing world. In the United States, breast cancer is the most common non-skin cancer and the second leading cause of cancer-related death in women. In the past fifty years, a woman's lifetime risk of breast cancer more than tripled in the United States, to one in seven today. This trend parallels a staggering increase of chemicals in the environment. Given the increasing number of women in the workforce, it is possible that increases in breast cancer incidence may be caused by occupational exposure.

Methods: Application of literature review results of breast cancer risk factors and screening efforts at workplaces to determine the cost-benefit analyses for applications in an occupational medicine practice.

Results: Review of epidemiologic studies on suspected environmental risk factors for breast cancer shows that at risk populations can readily be found in the workplace. Effective screening efforts by occupational medicine physicians can reduce mortality in the workforce. Although, conclusions drawn here are limited, it is advisable to develop national policies to reduce chemical exposures that may be associated with breast cancer.

Conclusions: Occupational physicians may be an important and appropriate healthcare provider with the opportunity to screen on at risk population, (workforce- female from 18- 65) and influence a wide range of well established and suspected environmental risk factors for breast cancer by incorporating prevention into occupational medicine clinic visits. Mammography and the clinical breast exam have a potential to detect suspicious lesions and may be implemented in occupational medicine clinics. Integrating screening into pre-employment or periodic examinations would expend minimal time and reasonable expenses while potentially preventing worker mortality. The integration of breast cancer screening into occupational medicine may simultaneously improve worker health and increase the value of the occupational medicine physician.

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1.0 INTRODUCTION

In the United States, breast cancer is the most common non-skin cancer and the second leading cause of cancer-related death in women, although each year, a small number of men are diagnosed with or die from breast cancer. The breast cancer diagnosis rate has increased, however the overall breast cancer death rate has dropped steadily since the early 1990s. The incidence of breast cancer is highest in Whites and African Americans have higher mortality rates than any other racial or ethnic group in the United States. The gap in mortality between African Americans and Whites has widened in recent years. (NIH, 2007) The estimated new cases and deaths from breast cancer in the United States in 2008 are 182,460(female); 1,990 (male) and 40,480 (female); 450 (male) respectively. (table 1) (American Cancer Society, 2008)

In terms of the absolute number of incident cases, breast cancer now ranks first not only in the industrialized world but also in the developing world. The worldwide mortality figure for the year 2000 was 370,000. However, there are marked geographical differences, with Africa and Asia currently having incidence rates some 10 times lower than those of North America and Northern Europe. Studies of migrant populations have long indicated that the genetic background only plays a tiny role in these differences. (DL Davis et al, 2003)

Table 1. Estimated New Breast Cancer Cases and Deaths by Sex, US

	Estimated New Cases			Estimated Deaths		
	Both Sexes	male	female	both sexes	male	female
2008	184,450	1,990	182,460	40,930	450	40,480
2007	180,510	2,030	178,480	40,910	450	40,450
2006	214,640	1,720	212,920	41,430	460	40,970
2004	217,440	1,450	215,990	40,580	470	40,110

Breast Cancer

Breast cancer, the result of out-of-control growth of cells of the breast, is a complex disease and there are more than 10 types of breast cancer. Eighty percent of all breast cancers are fueled by a natural hormone - estrogen. In vitro assays have identified approximately 250 chemicals that mimic or interfere with estrogen, which stimulates proliferation of estrogen-sensitive breast cancer cells in laboratory studies and presumably underlies many of the established breast cancer risk factor. (Brody JG et al, 2007)

Hormones seem to play a role in many cases of breast cancer, but just how this happens is not fully understood. Suggested DNA mutations related to breast cancer occur in single breast cells during a woman's life rather than being inherited. These acquired mutations of oncogenes and/or tumor suppressor genes may result from other factors, such as radiation or cancer-causing chemicals. So far, the cause of most acquired mutations that could lead to breast cancer remains unknown. Most breast cancers have several gene mutations that are acquired. (American Cancer Society, 2007)

1.1 Traditional –well established risk factors of breast cancer

Established risk factors are believed to be largely responsible for geographic variation in breast cancer rates , both internationally and within the United States. A pattern of elevated mortality rates for female breast cancer in the US extending from the Mid-Atlantic through the Northeastern states has persisted for many years. (DHHS, NIH, NCI, 2004) The following risk factors are considered well established:

Age :

The chance of being diagnosed with breast cancer goes up as a woman gets older.

(NIH, 2007)

Personal history ;

Breast cancer in one breast increases risk of getting this disease in the other breast.

Family history :

A woman's risk of breast cancer is higher if her mother, sister, or daughter had breast cancer, especially at a young age (before age 40). Having other relatives with breast cancer on either her mother's or her father's side of the family may also increase risk. (NIH, 2007)

Certain breast changes :

Having atypical hyperplasia or lobular carcinoma in situ increases the risk of breast cancer.

Genetic alterations :

An estimated 5 to 10 percent of all breast cancers can be attributed to inherited genetic factors. Changes in certain genes (BRCA1, BRCA2, and others) increase the risk of breast cancer. Some American women - many of whom are descendants of Ashkenazi Jews from

Eastern and Central Europe - have an inherited BRCA1 mutation. More than half will be diagnosed with breast cancer by age 50. In some BRCA1 families, there is a likelihood of developing both breast and ovarian cancers. The BRCA2 genetic mutation also is prevalent among families with Ashkenazi backgrounds. Genetic testing can sometimes show the presence of specific genetic changes that are related to risk among those with family history of breast cancer. Other genes that may be associated with breast cancer are : p53, AT, the GADD repair group, the RB suppressor gene, and the HER-2/neu oncogene. (NIH, 2007)

Reproductive and menstrual history :

The older a woman is when she has her first child, the greater her chance of breast cancer. Women who began menstruation at an early age (before age 12), went through menopause late (after age 55), or never had children also are at an increased risk. Women who take menopausal hormone therapy (either estrogen alone or estrogen plus progestin) for 5 or more years after menopause also appear to have an increased chance of developing breast cancer. Research has been done to determine whether having an abortion or a miscarriage affects a woman's chance of developing breast cancer later. Large, well designed studies have consistently shown no link between abortion or miscarriage and the development of breast cancer. (NIH, 2007)

Race :

Breast cancer occurs more often in white women than Latino, Asian, or African- American women.

Radiation therapy to the chest :

Radiation therapy to the chest before age 30 are at an increased risk of breast cancer. Studies show that the younger a woman was when she received radiation treatment, the higher her risk of breast cancer later in life. (NIH, 2007)

Breast density :

Older women who have mostly dense (not fatty) tissue on a mammogram are at increased risk of breast cancer.

DES (diethylstilbestrol) :

Women who took DES during pregnancy between 1940 and 1971 have a slightly increased risk of breast cancer. Daughters of women who took DES during pregnancy may have a slightly increased risk of breast cancer after age 40, also their risk is increased for vaginal cancer. (NIH, 2007)

Obesity :

Women who are obese, especially after the menopause have an increased risk of developing breast cancer because of abnormally high proportion of fat. Body makes some of its estrogen in fatty tissue, obese women are more likely than thin women to have higher levels of estrogen in their bodies. High levels of estrogen may be the reason that obese women have an increased risk of breast cancer. Also, some studies show that gaining weight after menopause increases the risk of breast cancer. Excess fat in the waist area may affect risk more than the same amount of fat in the hips and thighs. Researchers believe that fat cells in various parts of the body have subtle differences in their metabolism that may explain this observation. (NIH, 2007)

Physical inactivity :

Women who are physically inactive throughout life appear to have an increased risk of breast cancer. Being physically active may help to reduce risk by preventing weight gain and obesity.

Alcohol :

Some studies suggest that the more alcoholic beverages a woman drinks, the greater her risk of breast cancer. Alcohol decreases the body's ability to change estrogen into the inactive form and therefore, increases risk. (DHHS, NIH, NCI, 2004)

Oral contraceptives and HRT(hormonal replacement therapy).

Some studies have shown an increased risk of breast cancer in women taking oral contraceptives, while other studies have shown no change in risk. (NIH, 2007)

The Million Women Study in the United Kingdom revealed that all types of postmenopausal hormone replacement therapy significantly increased the risk of breast cancer, underscoring earlier findings from the Women's Health Initiative study in the United States. Another study found that use of HRT after previously being diagnosed with breast cancer tripled a woman's risk of recurrence or development of a new breast tumor.

Breast Cancer Fund, 2004)

Interestingly, most women who have these risk factors do not get breast cancer. Also, most women who develop breast cancer have no history of the disease in their families. Except for growing older, most women with breast cancer have no strong risk factors. (Lafranchi et al, 2007)

2.0 ROLE OF HORMONES IN DEVELOPMENT OF BREAST CANCER

Estrogen target tissues are breast, uterus and ovaries. It is essential for the normal growth and development these tissues and it is important for reproduction. It regulates a woman's menstrual cycles and also helps maintain healthy bones, heart. Estrogen can stimulate cell division directly by binding with its receptors. Indirect way of stimulating a cell division is more complex and involves levels of receptors of other hormones such as progesterone and growth factors. Since estrogen stimulates cell division, it can increase the chance of making a DNA copying error in a dividing breast cell. Estrogen can also have the effect of making a spontaneous or chemically-induced mutation permanent, since it influences the rate of cell division. Also, estrogen has been proved to promote breast tumors.

Stimulating the development of the breast ducts is an important normal function of estrogen. However, immature breast cells are particularly sensitive to the effects of carcinogens and are more likely to bind them. The immature stem cells are also less efficient at repairing damage to DNA caused by carcinogens. Stages when immature breast cells are particularly vulnerable to damage by carcinogens include 0- 4 years of age, and from puberty to a woman's first full term pregnancy. During pregnancy breast cells mature. These changes protect them against damage caused by carcinogens because they bind them less strongly and are more efficient in DNA repair than immature cells.(RA Clark et al, 2002)

The active estrogen made by the ovaries is metabolized by the liver into an inactive form which does not cause the breast cells division. Some of the estrogen is transformed into a long-acting that continues to stimulate the breast cells. Women's bodies differ in production of this long-acting estrogen, and therefore those who produce more have a higher breast cancer risk.(Lafranchi et al, 2007) The strongest form of estrogen made in vivo is called 17-beta estradiol (E2). Estradiol can be changed into other forms of estrogen that are not as strong. For example, the form of estrogen called 2-hydroxyestrone (2-OHE) is a weak estrogen, while the form called 16-alpha-hydroxyestrone (16a-OHE) is a stronger estrogen. There is a concern that the 16a-OHE form of estrogen can cause normal breast cells to become cancerous. In some in vitro breast cancer studies, cells have been exposed to different environmental contaminants to see if they make different amounts of the 16a-OHE and the weaker 2-OHE forms of estrogen. Exposure to chemical such as insecticide DDT and the herbicide atrazine, caused the cells to make comparatively more of the 16a-OHE form of estrogen that may promote the formation of breast tumors. (RA Clark et al, 2002)

Another hormone implicated in breast cancer development is thyroid hormone. In a retrospective case-control study of 2,226 females, researchers found that women with primary hypothyroidism had a 61 percent lower risk of developing invasive breast cancer. Additionally, women newly diagnosed with breast cancer were 57 percent less likely to have under-active thyroid gland condition compared to a control group of healthy women. Additionally, breast cancer patients in the study who also had a history of hypothyroidism tended to be older when diagnosed and had a less aggressive, slower-progressing type that was sensitive to estrogen treatment.

Nuclear receptors for thyroid hormone and estrogen are part of the "superfamily" of receptors that contribute to control cell growth and differentiation. Hormones must bind to this family of important proteins to exert their functions, and depending on the hormone to which they bind, can either stimulate or inhibit the growth of cells. Thyroid hormone and estrogen both share similar pathways in regulating proliferation and growth in the target cells, including cancer cells. This well known phenomenon of cross-talk between the receptor of these hormones may promote or inhibit thereby determining the "fate" of a cell towards either a regulated growth or a cancer. Data suggest a possible biologic role for thyroid hormone in the etiology of breast carcinoma and indicate areas of research for the prevention and treatment of breast carcinoma. (Cristofanilli M et al, 2005)

Environmental estrogens or xenoestrogen are naturally occurring (e.g. phytoestrogens in plants) or synthetic chemicals that can act like human estrogen made by the ovary. The greatest concern is over synthetic xenoestrogens that are not easily broken down, and that can accumulate and be stored in the fat cells, including breast fat. The strength of these xenoestrogens varies; some are ten times weaker than human estrogen, while others are a million times weaker. Some xenoestrogens increase cell division and thus may contribute to breast cancer risk. (RA Clark et al, 2002)

Xenoestrogens include: Bisphenol-A, used in plastic food containers and baby bottles; polyvinyl chloride (PVC), used extensively in food packaging, as well as in medical products, appliances, cars, toys, credit cards and rainwear; pesticides (including some forms of DDT) in agriculture; and diethylstilbestrol, a drug prescribed to pregnant

women from 1941 to 1971 that doubled the risk of breast cancer for women who were exposed to it in utero and who are now over 40 years of age.(Breast Cancer Fund, 2004)

Other chemicals identified as being weak environmental estrogens include food preservatives (BHT and BHA), the industrial detergent by-products nonyl- and octaphenol, compounds used in plastics, the food dye Red #3, and the solvent formaldehyde which was used in carpet manufacturing, and is still used in making plywood.

There are many unanswered questions about xenoestrogens and breast cancer risk. More studies are needed to identify which environmental chemicals are xenoestrogens, to determine their strength, since very weak xenoestrogens may not stimulate breast cell division. Studies to determine the extent of exposure to xenoestrogens in the home, workplace, and environment are also needed.

There are other chemicals that are not environmental estrogens and affect the levels of and types of estrogen in the body. They may affect estrogen metabolism, or they may affect the levels of other hormones in the body that control the production and release of estrogen from the ovary. Researchers are now examining the amounts of 16a-OHE and the weaker 2-OHE forms of estrogen in the urine of women with and without breast cancer to see if there is any relationship to breast cancer risk. A recent study has shown that postmenopausal women with breast cancer have a significantly lower amount of the weaker 2-OHE estrogen versus the 16a-OHE estrogen compared to postmenopausal women without breast cancer. Women with higher levels of the 16a-OHE estrogen in their bodies were more at risk for developing breast cancer. (RA Clark et al, 2002)

3.0 ENVIRONMENTAL RISK FACTORS OF BREAST CANCER

Evidence from Epidemiologic environmental pollutants studies

As many as 50 percent of breast cancer cases remain unexplained by personal characteristics and other traditionally-accepted risk factors; epidemiologists and other scientists increasingly believe many cases are linked to environmental factors. (Breast Cancer Fund, 2004) In the past fifty years, a woman's lifetime risk of breast cancer more than tripled in the United States, to one in seven today. This trend parallels a staggering increase of chemicals in the environment: some of the 85,000 synthetic chemicals in use today can be contributing to breast cancer by altering hormone function or gene expression.

Laboratory research identified 216 chemicals among those - environmental pollutants that cause breast tumors in animals and may contribute to breast cancer risk by damaging DNA, promoting tumor growth, or increasing susceptibility by altering mammary gland development. A total of 73 have been present in consumer products or as contaminants in food, 35 are air pollutants, 25 have been associated with occupational exposures, 29 are produced in the United States in large amounts, often exceeding 1 million pounds per year. Compounds of interest include, for example, benzene from gasoline, polycyclic aromatic hydrocarbons from vehicle exhaust and air pollution, disinfection products from chlorinated drinking water, polychlorinated biphenyls, dioxin, chlorinated solvents, and some pesticides. (Brody JG et al, 2007)

3.1 Polycyclic Aromatic Hydrocarbons (PAH)

Formation of PAHs is mainly caused by incomplete combustion of carbon-containing fuels such as wood, coal, diesel, fat, tobacco, or incense . PAH mixtures and some individual PAH chemicals, such as benzo(a)pyrene, are mammary carcinogens in laboratory animals. The IARC has evaluated soot and other PAH mixtures as known human carcinogens, based primarily on lung and skin cancers, and has identified individual PAHs as probable human carcinogens. Major sources of exposure for general populations are smoking, air pollution, auto exhaust, diesel, and diet. Dietary sources include smoked and grilled foods and foods such as grain that are contaminated by ambient air pollution. PAHs have been found in coal tar production plants, coking plants, bitumen and asphalt production plants, coal-gasification sites, smoke houses, aluminium production plants, coal tarring facilities, and municipal trash incinerators.

Air pollution and vehicular exhaust also contain numerous other chemicals, including some identified as mammary carcinogens or as endocrine disrupting compounds that may affect breast cancer risk. Workers may be exposed to PAHs by inhaling engine exhaust and by using products that contain PAHs in a variety of industries such as mining, oil refining, metalworking, chemical production, transportation, and the electrical industry. (ATDSR, accessed 12/1/07)

Metabolites of pyrene and DNA adducts have been used as biomarkers of high level exposure to PAHs and these biomarkers are also valid markers of low level

environmental exposure to PAHs. It was suggested that they should be implemented in combination with more traditional techniques for the assessment of general population exposure to PAHs from ambient air pollution. (Castano-Vinyals G et al, 2004)

Susceptibility due to genetic polymorphisms that affect DNA repair in interactions with PAH exposure has been examined in case-control studies. The Long Island breast cancer study is a large population-based study of an association between PAHs and breast cancer. Exposure assessment relied on a measure of DNA damage in blood drawn near the time of diagnosis. The OR for detectable versus non detectable adducts was 1.32 (95% CI, 1.00–1.74). Women with the highest compared with lowest PAH-DNA adducts had an approximately 50% higher breast cancer risk (OR=1.51, 95% CI, 1.04-2.20), with little or no evidence of substantial confounding because of taking into account an extensive list of breast cancer risk factors. The results did not show a dose-response relation. However, dose may not be well characterized in this study, despite the use of biological measures, because measurements taken after diagnosis may not be representative of the etiologic period, and they do not consider the effects of DNA repair mechanisms. The relative contributions of environmental sources, active and passive smoking, diet, and air pollution—to adduct formation in this study population are unclear because of inconsistent association. (Gammon MD et al, 2002)

Shen et al, 2005 reported a statistically nonsignificant additive interaction between the DNA base excision repair gene XRCC1 399 Gln allele carriers and PAH-DNA adducts, only among never smokers (OR = 1.92; 95% CI, 1.2–3.1) with exposure and mutant genotype), and no evidence of interaction for codon 194Tr carriers.

Using the population based breast cancer case-control study on Long Island, NY, Terry et al, 2004 reported a joint effect of XPD Gln/Gln genotype and adduct levels above the median (OR = 1.9; 95% CI, 1.15–3.15) versus Lys/Lys genotype and adducts below the median. this study suggests that those individuals with this polymorphism in the XPD gene may face an increased risk of breast cancer from PAH-DNA adducts and cigarette smoking. Tang et al, 2003 in a much smaller study, found XPD alleles were associated with adduct levels in tumor but not nontumor or benign tissue, suggesting a possible role in tumor progression. Rundle et al, 2002 found the null variant of the detoxifying gene GSTM1 was associated with adduct levels in cases, but not controls. Results suggest that the GSTM1 polymorphism plays a role in preventing accumulation of environmental damage in breast tissue. Although these results suggest that molecular epidemiology may reveal the mechanisms for an association between environmental PAH exposure and breast cancer, it will be important to see whether the findings are repeated and extended in other studies.

Two studies relevant to PAHs assessed exposure from residential location together with geographic models of air pollution. Bonner et al, 2005 in a study that obtained data from the New York State Department of Environmental Conservation for Erie and Niagara Counties reported a statistically significant trend (P-trend <.05) for higher breast cancer risk among premenopausal and postmenopausal women whose birth address was near a monitoring location with higher levels of total suspended particulates (TSP) measured since the 1960s. Among postmenopausal women, ORs were found to be elevated but statistically unstable for higher TSP at birth, menarche, and first full-term pregnancy. The lack of an association at menarche and first full-term pregnancy for

premenopausal women could be due to lower TSP levels in recent years, shorter lag time, or other factors. Study suggests that exposure in early life to high levels of PAHs may increase the risk of postmenopausal breast cancer; however, other confounders related to geography cannot be ruled out.

Using indicators of industrial density (chemical, metal fabricating, and other specific types of industry) and traffic density over a 20-year period, Lewis-Michl et al, 1996 reported higher risk associated with living in areas with air pollution from industrial facilities, with the OR excluding 1 for Nassau County (OR = 1.61; 95% CI, 1.06–2.43), but not Suffolk County on Long Island, NY. Results for living near high-density traffic were inconsistent.

3.2 Persistent Organochlorines

Persistent organochlorine compounds include PCBs, chloroforms, trichlorethylene, vinyl chloride, pesticides, insecticides, such as DDT. They are environmentally persistent and lipophilic. They are frequently detected in food, soil, and dust, concentrate up the food chain, and are found in human breast milk and adipose tissue. Residues can be measured in blood and breast tissue, providing a way to quantify exposure, although these measures are invasive and expensive; therefore, as a practical matter, levels cannot be measured repeatedly in an individual. Specific organochlorine compounds, such as for example dieldrin, exhibit varying estrogenic activity. Organochlorides, including dioxins, can be naturally produced in the high temperature environment of forest fires, and dioxins have been found in the preserved ashes of lightning-ignited fires that predate synthetic dioxins.

Polychlorinated biphenyls (PCB)

PCB mixtures have been used for a variety of applications such as dielectric fluids for capacitors and transformers, heat transfer fluids, hydraulic fluids, lubricating and cutting oils, and as additives in pesticides, paints, carbonless copy paper, adhesives, sealants, plastics, reactive flame retardants, and as a fixative for microscopy. They were also used in surgical implants. Their production was banned in

the U.S. in the 1970s. Because of bioaccumulation in contaminated rivers in industrial areas, the primary source of exposure in general populations is from fish. PCBs accumulate in fat and high levels have been found in human breast milk. The US EPA and the IARC have determined that PCBs are probably carcinogenic to humans. PCBs have been associated with estrogenic, tumor promoting, and immunosuppressive activities, all of which are relevant in the development of breast cancer. (Negri E. et al, 2003).

Several articles examined the association between PCBs and breast cancer in case-control and nested case-control studies. The primary outcome was incident breast cancer, some studies examined breast cancer recurrence, survival, or aggressiveness. Exposure measures included concentrations of total PCBs, congeners grouped by functional significance, and individual congeners assessed in blood or adipose tissue.

In nine studies, of organochlorine exposure and risk of breast cancer in general populations, the evidence for an association between total PCB and cancer was inconsistent, regardless of the exposure measure.(Wolff MS et al, 2000, Laden F et al, 2002, Zheng T et al, 2000, Raaschou-Nielsen O et al, 2005) No association has been observed in studies that used a PCB congener grouping based on enzyme induction and other toxicological aspects. (Moysich KB et al, 2002, Ward EM et al, 2000)

The most consistent evidence for the association between PCB exposure and breast cancer risk come from studies of genetic polymorphisms effect. PCB exposure induces CYP1A1 activity and metabolizes steroid hormones, polycyclic aromatic hydrocarbons in humans. PCBs themselves or other xenobiotics can be metabolized to carcinogenic intermediates in the presence of the variant genotype (Laden F et al, 2002).

The modifying effect of a polymorphism on the association between PCB and breast cancer risk has been most pronounced in the cytochrome P450-1A1(CYP1A1) gene levels. Three studies have found a higher breast cancer risk associated with higher PCB exposures among postmenopausal white women with the CYP1A1-m2 genetic variant exposures among postmenopausal white women with the CYP1A1-m2 genetic variant (also referred to as the exon 7 variant). (Zhang Y et al, 2004, Moysich KB et al, 1999, Laden F et al, 2002)

In contrast, Li et al, 2005 found a non-significant risk increase among premenopausal women with the CYP1A1-m2 variant, but not among postmenopausal women, based on smaller numbers than in the other studies. Genotype frequencies for *CYP1A1* M1- and M3-containing genotypes were higher among African Americans than among whites, whereas M2- and M4-containing genotypes were more prevalent among whites. Another small study demonstrated a non-significant risk elevation among women with the CYP1A1-m1 variant genotype and high PCB levels. However, in general data do not support the hypothesis that organochlorines increase the risk of breast cancer among subgroups of women with specific metabolic genotypes. (McCready et al, 2004)

Potential effect of environment on p53 gene mutation was reported by Hoyer et al, 2002 in the study of women with variants of the p53 suppressor gene. The highest quartile of total PCB exposure was associated with increased risk of breast cancer (OR=3.0; 95% CI= 0.66–13.62). In the study of mechanisms of susceptibility of xenobiotic enzymes, results from Helzlsouer et al, 1999 case-control study nested in a prospective cohort did not reveal modifying effects of the GSTM1, GSTT1, GSTP1, COMT, and CYP17 genotypes on the association between PCB levels and breast cancer risk.

Following three studies have associated high PCB exposure to breast cancer recurrence or survival. Muscat et al, 2003 found that high PCB levels were associated with an increased risk of breast cancer recurrence (OR = 2.9; 95% CI= 1.02–8.2). Hoyer et al, 2000 reported that high PCB levels are significantly associated with risk of death among women with estrogen receptor positive (ER1) tumors (OR = 2.5; 95% CI, 1.1–5.7), and Demers et al, 2002 found that higher levels of PCB were associated with more aggressive breast cancer. These studies provide high level of confidence in the validity of the exposure measure because of the shorter time interval between exposure and outcome, and also suggests the possibility that ongoing exposures may have health implications.

Dioxin

Tetrachlorodibenzo-p-dioxin (TCDD) has no useful purpose and is produced as the unwanted by-products of industrial processes such as the manufacture of PVC, pesticide production, incineration, pulp and paper bleaching with chlorine, and the smelting and recycling of metals. It is classified by the International Agency for Research on Cancer (IARC) as a human carcinogen, based on an increase in cancers at all sites, and has multiple endocrine effects. TCDD is a reference chemical for mixtures of dioxins and furans produced by combustion and other processes involving chlorine.as reviewed by Steenland et al, 2004. Dioxin dissolves easily in fats and as a result can build up in the fatty tissues of animals and humans. So animals with high fat contents, such as humans, whales, polar bears and dolphins, are particularly susceptible to the build up of dioxin.

Primary sources of exposure are dietary fat, particularly milk, fish, and meat (Kogevinas et al, 2001). Schecter et al, 1994 estimated that nursing babies exceed the U.S. and European standards for safe dose of TCDD in their first year of life.

The best evidence of the association between dioxin and breast cancer comes from two studies done in Italy and Russia. The first cohort are community residents exposed in 1976 by industrial accident in Seveso, Italy. The most recent report from the Seveso accident includes 981 women who were infants to 40 years of age at the time of the accident and lived in the two most contaminated zones. (Warner M et al, 2002) TCDD was measured in serum collected between 1976 and 1981 and standardized to represent 1977 levels. Results showed a 2- fold increase in breast cancer incidence in 1976 to 1998 associated with a 10-fold increase in serum TCDD, based on 15 cases in a cohort of 981 women. Bertazzi PA et al, 1993 followed-up cohort in 15- year mortality study that assessed exposure by zone of residence and showed non-significantly lower breast cancer incidence through 1986 among older women (RR = 0.7; 95% CI, 0.3–1.5)⁵² and lower mortality through 1991. This cohort will continue to provide information on breast cancer risk association with dioxin because these women are still young.

The second cohort comes from the occupational exposure in a chemical plant in Chapaevsk, Russia. This cohort of workers have been exposed during production of herbicides. Revich et al, 2001 reported elevated breast cancer mortality (SMR = 2.1; 95% CI, 1.6–2.7) among women living near the chemical plant compared with surrounding regions.

In an early report by Manz et al., 1991 on a cohort of German herbicide workers, showed elevated female breast cancer mortality, although only 7% of the women workers were in the high exposure locations. Flesch-Janys D et al, 1999 follow-up reports from this cohort used a more sophisticated exposure model based on biological measures and integrating exposure over time. The incidence was found to be significantly elevated (standardized incidence ratio [SIR] = 1.84; 95% CI, 1.17–2.67) in comparison with the regional population. .

Only one study, Warner et al, 2002 of breast cancer and dioxin, was adequately controlled for confounding by established risk factors. Kogevinas et al, 1997 compared exposed women and a similarly employed nonexposed group and Flesch-Janys et al, 1999 compared risk across exposures within the cohort. Both strategies reduce potential confounding. Comparisons of occupationally exposed women with general populations are problematic because women factory workers likely differ from white and pink-collar workers and nonemployed women with regard to many factors related to breast cancer.

Dichloro-diphenyl-trichloroethane(DDT)/Dichloro-diphenyl-dichloroethylene(DDE)

DDT is a pesticide once widely used to control insects. It is a white, crystalline solid with no odor or taste. DDE levels are considered a measure of exposure to DDT and to DDE from food and the environment, with DDE being the predominant exposure in the U.S. since 1972, when DDT was banned, but is still used in some countries . DDE (dichlorodiphenyldichloroethylene) and DDD (dichloro-diphenyl-dichloroethane) are chemicals similar to DDT that contaminate commercial DDT preparations.

In the early 1990s positive findings triggered new investigations, however reviewed studies of DDT/ DDE and dieldrin by Snedeker et al, 2001, Moysich et al, 1999 and Negri et al, 2003 concluded that existing research strategies in 2002 through 2003 provided conflicting and mostly negative evidence. From 2006 research provides potential new evidence regarding PCBs, new findings for dioxin, essentially unchanged conclusions for DDT/DDE, and a few new results for other organochlorine pesticides.

Twenty-five reports from case-control studies and nested case-control studies published in 2000 to June 2006 examined associations between serum or adipose levels of DDT or DDE and breast cancer. A key limitation of the biological markers of organochlorine such as DDT/DDE exposure is that they may not accurately measure or rank exposure during the years when a tumor was initiated or during critical exposure periods in the life cycle when susceptible developing breast tissue was at risk To date, blood and adipose techniques are not useful in assessing exposure to nonpersistent current-use pesticides. The challenge in studies of these compounds is that exposure is usually episodic, so many measurements over a long time would be needed to accurately rank subjects on exposure and this cannot be done retrospectively because the new pesticides are nonpersistent and no permanent marker of their effect has been identified. (Snedeker SM et al, 2001, Birnbaum et al, 2003)

Internationally, a few studies showed elevated risk. In two hospital-based case-control studies, Charlier et al, 2003, 2004 reported higher risk in European whites with detectable DDT (OR = 5.64; 95% CI, 1.81– 17.65) or DDE (OR = 2.21; 95% CI, 1.41– 3.48) in serum. Romieu et al, 2001 found evidence of a dose-response association (P-trend <.02) with DDE in serum (highest compared with lowest quintile OR = 3.81; 95%

CI, 1.14–12.8) in Mexico City. Most studies did not support an association of DDE and breast cancer overall or stratified by menopausal status, tumor hormone receptor status, parity, breastfeeding, or body mass index.

In the US, NIH sponsored one of the largest of the organochlorine studies. The Long Island population-based case-control study by Gammon MD et al, 2002 found no association between breast cancer risk and the exposure. Similarly, two meta-analyses, Laden F et al, 1988 and Lopez-Cervantes M et al, 2004 of the organochlorines did not demonstrate an elevated risk. These findings doesn't support the idea to investigate association of breast cancer occurrence and measurement of organochlorine levels near the time of diagnosis.

The promising, although not consistent results are coming from studies of polymorphism in metabolism and detoxification of xenobiotics. Demers et al, 2000 study investigated breast cancer aggressiveness and found a dose related increased risk for DDE and large tumors with lymph node involvement in a hospital-based case control study. Studies of disease progression have the advantage that biological measures taken near diagnosis are more plausibly indicative of exposure during a time relevant to the outcome studied.

From 2000 to June 2006 twenty-one studies reported on 14 organochlorine pesticides other than DDT and DDE. Each has been linked to higher risk in at least one of the studies. In a nested case-control study of Danish women that averaged 2 serum measurements of dieldrin from 1976 and 1983. Hoyer et al, 2000 reported a dose-related increased risk of ER negative tumors (OR =7.6; 95% CI, 1.3–4.6 for highest quartile), but not ER positive tumors. Also, there was an evidence of elevated mortality in women

with ER positive tumors. Study revealed an interaction between higher dieldrin levels and a variant of the p53 suppressor gene, although the effect did not reach statistical significance.(Hoyer et al, 2002) In another study Hoyer et al, 2001 found a dose-related increased risk of death with higher dieldrin exposure (OR = 4.6; 95% CI, 1.8–11.5 for highest quartile.

Long Island study by Gammon et al, 2002 was inconsistent to confirm the increased risk with dieldrin exposure and also, .Muscat et al,2003 found statistically unstable elevated risk of recurrence associated with hexachlorobenzene, beta-hexachlorohexane, and transnonachlor. Raaschou-Nielsen et al, 2005 found a relative risk of breast cancer below one in the cohort of Danish women examining the adipose tissue . Demers et al, 2000 found associations between tumor size and lymphnode involvement for beta- HCH, oxychlordane, and transnonachlor.

Given the limitations of already mentioned biomarkers for organochlorines and their measurements, it is essential to explore other exposure assessment tools for the many pesticides (and other compounds) that are hormonally active or shown to be mammary gland carcinogens.

Residential location and job histories have been the primary alternatives. Residential location has the advantage that people spend much of their time at home and occupational studies have the advantage of assessing higher exposures than general populations.

Several studies used the California Department of Pesticide Regulation (DPR) database to assess residential or occupational exposure, based on date, location, and other characteristics of pesticide application. A cohort study among California teachers found no association between breast cancer and exposure estimates based on California

pesticide reporting data, (Reynolds P et al, 2004) but California began detailed recording of pesticide use only recently (1990), so effects with long latency could not be assessed. In a nested case-control study of New York state women, O’Leary et al, 2004 found some evidence of increased risk for women living on formerly agricultural land (OR = 1.5; 95% CI, 0.8–2.9), based on 20 cases, and higher risk for women age 26 years and older at the birth of their first child (OR = 6.4; 95% CI, 2.2–18.2, based on 14 cases), suggesting a possible interaction with susceptibility due to late differentiation of the mammary gland, which occurs during the first pregnancy. Case-control study of agricultural workers did not find consistent associations, although there was (nonsignificantly) higher risk among younger women with the highest chemical exposures. (Mills PK et al, 2005)

Historically, there have been developed questionnaire-based exposure assessment for traditional breast cancer risk factor such as diet, tobacco use, physical activity, pharmaceutical hormone use, childbearing, lactation, menstrual history, postmenopausal obesity and weight gain, family history of breast cancer, and other possible breast cancer risk factors. However, effort to develop these methods for environmental pollutants surprisingly are still insufficient.

The Agricultural Health Study by Mills PK et al, 2005 is an important exception, with extensive methods developed to ensure the validity of self-reported pesticide use in this study. The results provide some evidence of higher risk for farm wives living closest to crops (OR = 1.4; 95% CI, 0.9–2.0) and for wives whose husbands reported use of organochlorines (OR = 1.3; 95% CI, 0.9–2.0) or 2,4,5-TP (OR = 2.0; 95% CI, 1.2–3.2). Additional follow-up in this cohort will likely be one of the best sources of information on effects of current-use pesticides.

Contradictory to the above study, in the Carolina Breast Cancer a population- based case control study by Duell et al, 2000 found that farm women did not have higher risk overall. Women who reported their presence in a field during or shortly after pesticide application were at higher risk compared with farming women who were not exposed (OR = 1.8; 95% CI, 1.1–2.8), but their risk was similar to women who had never farmed. Women who reported they did not use exposure protection when applying pesticides had a higher risk when compared with women who said they did not apply pesticides (OR = 2.0; 95% CI, 1.0–4.3), but the study may have been susceptible to recall bias.

Important contribution to breast cancer investigation are studies that identify environmentally sensitive breast changes such as the Crete study by Dolapsakis G et al, 2001 of women who went for mammograms in Crete. Those who worked with organophosphate and organocarbamate pesticides in greenhouses were at significantly higher risk for a variety of nonmalignant breast conditions. Among exposed women the rate of malignancy was significantly higher in women ages 40 to 49 years than older women.

Although, an inconsistent and mostly negative picture arose from evaluation of the studies regarding organochlorine pesticides to date, there is good chance to receive important information because widespread exposure of girls and women began in the late 1940s, so women with early-life organochlorine exposure are now in their 50s. Therefore, following this birth-cohort over the next 20 years with methods that attempt to capture developmental exposures is important.

3.3 Drinking Water Disinfection Byproducts

Chlorine is a very active substance and it reacts with naturally occurring substances to form compounds known as disinfection byproducts (DBPs). Drinking water disinfection byproducts (DBP) have been the subject of numerous cancer assessments, including a small number of studies that reported on breast cancer. The most common DBPs formed when chlorine is used are trihalomethanes (THMs), and haloacetic acids (HAAs).

MX- 3-chloro-4-(dichloromethyl) -5-hydroxy-2(5H) -furanone, a major mutagenic constituent of DBP, is a cause of mammary tumors and this evidence suggests that breast cancers should be investigated as well. (WHO , 2000)

Most of the studies of drinking water and breast cancer suffer from poorly controlled confounding and study design. Exception is case-control study done by Aschengrau et al, 2003 that is reporting on accidental exposure to perchloroethylene in drinking water from distribution pipes. This only population-based study showed that increase in risk was not monotonic (adjusted OR = 1.6; 95% CI, 1.1–2.4 for exposure >75th percentile). Some misclassification within the exposed group possibly happened because the assessment is based on a model of the water distribution system; however, participants classified as unexposed were unlikely to be exposed from other water sources, a strength in this study that is uncommon in studies of environmental pollutants. Possible confounders were extensively evaluated. The results of the study suggest that women with the highest PCE exposure levels have a small to moderate increased risk of breast cancer.

Morris RD et al, 1999 meta-analysis of case-control studies yields a relative risk of 1.18 (95% CI, 0.90- 1.54) associated with chlorinated drinking water; the power to detect a RR of 1.20 at $P < .05$ was 0.27. Only 4 of 12 studies in the meta-analysis reported on breast cancer. The availability of water quality records dating to the passage of the Safe Drinking Water Act in 1974 may provide underutilized opportunities to investigate a variety of environmental pollutants and breast cancer at varying geographic scales.

3.4 Organic Solvents

Common uses for organic solvents are in dry cleaning (e.g. tetrachloroethylene), as paint thinners (e.g. toluene, turpentine), as nail polish removers and glue solvents (acetone, methyl acetate, ethyl acetate), in spot removers (e.g. hexane, petrol ether), in detergents (citrus terpenes), in perfumes (ethanol), and in chemical syntheses, fuel additives (ethylene glycol, methyl ether). These organic solvents were found to sensitize breast tissue cells to the effects of hormones estrogens and progestins, therefore increasing the risk of breast cancer. Detection of organic solvents in breast milk confirms their availability to breast tissue. A number of organic solvents, including common chlorinated solvents, such as methylene chloride, have been identified as mammary gland carcinogens. Exposure is common in the workplace and at lower levels from air, drinking water, and consumer products. Labreche et al, 1977 hypothesize that organic solvents or their metabolites initiate or promote breast carcinogenesis through genotoxic or similar mechanisms.

Hypothesis-generating ecologic study of Toxics Release Inventory (TRI) data and breast cancer in Texas counties is an example of methods that may identify directions for future research. The study found significantly higher incidence associated with 10 of 12 pollutants. (Coyle YM et al, 2005) Analysis indicated that formaldehyde, methylene chloride, styrene, tetrachloroethylene, trichloroethylene, chromium, cobalt, copper, and nickel were positively associated with the breast cancer rate. In multiple regression models, styrene releases were significantly associated with county-level breast cancer

rates for women and men, women, and women age older than 50 years, explaining 9% to 14% of variance. Analysis were controlled for age, race, and Hispanic ethnicity, but it would be useful to know whether variation in TRI exposures among Texas counties is strongly correlated with income, education, and reproductive patterns. Styrene was the most important environmental toxicant positively associated with invasive breast cancer incidence in Texas, likely involving women and men of all ages. It is used in the synthetic rubber industry, plastics manufacturing (including production of polystyrene food packaging), and is in resins, coatings, paints, tobacco smoke, food, building materials, and consumer products. Texas ranks first among states in TRI reported styrene releases.

3.5 Occupational studies

Given the increasing number of women in the workforce, it is possible that increases in breast cancer incidence may be caused by occupational exposure to hazardous agents. (Labreche et al, 1997)

Occupational literature also remains inadequate to evaluate the association between organic solvents and breast cancer and the gap becomes obvious analyzing the Environmental Health Perspectives 1996 monograph. Nine articles from major epidemiologic studies on benzene that have been reviewed (mammary carcinogen in animals) contained no reference to breast cancer. Also, historically fewer women than men have been employed long-term in industrial jobs characterized by relatively well-defined chemical exposures, and occupational studies have focused on men, thus providing little information regarding breast cancer risks in women.

Industries using solvents:

In one of the best-designed studies, Hansen et al, 1999 found an elevated risk of breast cancer diagnosis in a population of young women (age <55 years) for all jobs with extensive exposure to solvents, and more elevated risk was associated with longer duration of employment and longer lag times, as would be expected for a causal relation. Risk was approximately doubled for women with more than 10 years in an exposed job and 15 years lag time (OR = 1.97; 95% CI, 1.39–2.79). Perchloroethylene is a common dry cleaning solvent, so elevated risk among these workers is consistent with the Aschengrau et al, 2003 drinking water study. Gardner et al, 2002 found elevated

incidence associated with potential exposure to solvents in leather and fur processing (OR =3.25; 95% CI, 1.11–9.53) and to solvents and dioxin in glass manufacturing, in which risk was found to be more elevated among premenopausal women (OR= 2.70; 95% CI, 1.20–6.05).

Blair et al, 1998 found elevated risk among women who worked with solvents in aircraft maintenance (RR = 1.6; 95% CI, 0.9–2.8), and risk was higher for jobs in which workers were exposed to freon, solder flux, isopropyl alcohol, trichloroethane, toluene, methyl ethyl ketone, and methylene chloride. Many of the specific solvents were correlated with each other, reducing ability to attribute risk to particular compounds. In a retrospective cohort study, Rennix et al, 2005 found higher risk among U.S. Army enlisted women in jobs with likely medium or high solvent exposure (IRR =1.48; 95% CI, 1.01–2.07). Women in the Army are employed more frequently in non-traditional, industrial jobs such as auto mechanic and motor transport operators than in the general US population, increasing the probability of exposure to industrial chemicals.

Band et al, 2000 in a registry-based case control study of Canadian women, found elevated incidence among pre- and postmenopausal women in the food industry (OR=3.86; 95% CI, 1.06–14.1) and dry cleaning (OR = 5.25; 95% CI, 1.41–19.5). The results of this study suggest excess breast cancer risk notably in occupations using solvents and pesticides.

In a review, Goldberg et al, 2007 found limited evidence of higher risk among women in the pharmaceutical industry and beautician trades and little support for increased risk in textile workers or dry cleaning.

Chang et al, 2003 reported higher incidence in a large cohort of electronics factory workers in Taiwan. However, most of the women had been employed less than 1 year and 40% had been employed for less than 1 month, may bias the cancer risk toward false positive. This suggests no evidence that exposure to chlorinated organic solvents at the electronics factory was associated with elevated human cancers, although this cohort may yield more useful information in the future.

The two assessments of occupational exposure to PAH, benzene and gasoline, vehicular exhaust reported elevated risk of female (Petrallia SA et al, 1999) and male (Hansen J et al, 1999) breast cancer. Men who worked for more than 3 months in an exposed job were particularly at risk if their first exposure was before 40 years of age (OR = 3.7; 95% CI, 1.7–7.9 with no lag time; OR = 5.4; 95% CI, 2.4–11.9 with 10 years lag time).

Hairdressers:

Lamba et al, 2001 found slightly higher mortality among black (OR = 1.15; 95% CI, 0.98–1.30) and white (OR = 1.10; 95% CI, 1.03–1.17) women hairdressers in the U.S., and Pollan et al, 1999 found higher risk among Swedish women who were hairdressers in 1960 and 1970 (RR = 1.27; 95% CI, 1.11–1.47).

Nursing and laboratory work:

Several studies have assessed risks in nursing, health and science laboratories, which involve exposures to solvents, therapeutic agents, and the sterilant, ethylene oxide, which is a mammary gland carcinogen in animals. However, there is a need to find studies of nurses in which findings for chemical exposures are unlikely to be confounded by established breast cancer risk factors.

In reports from the last 10 years, Band et al, 2000 found elevated risk for nurses in British Columbia (OR = 1.54; 95% CI, 1.05–2.28).

Gunnarsdottir et al, 1995 found similarly elevated risk among Icelandic nurses (SIR = 1.52; 95% CI, 0.96–2.28 for nurses with 20 years experience) and higher risk with lag times of 30 years and longer (SIR = 3.30; 95% CI, 1.12–7.18 for 50 years of lag time). They report that nurses were similar to the national comparison population in number of children and age at first birth.

In a study specific to ethylene oxide, Norman et al, 1995 found an approximately 2-fold increased risk (SMR ranged from 2.55 (95% CI: 1.31-4.98, P = 0.02) to 1.70 (95% CI: 0.89-3.23, P = 0.09)) in women who worked in a plant with documented exposure. The excesses in observed breast cancer incidence diminished over time.

3.6 Epidemiologic environmental pollutants studies: Conclusion

Weaknesses and limitations

Limitations found in general include inadequate exposure assessment, lack of access to highly exposed and unexposed populations, lack of preclinical markers to identify associations that may be obscured by disease latency. Existing technologies are expensive to apply in studies large enough to reliably detect the modest risks typical of the established breast cancer risk factors.

The methodological weaknesses are recognizable in many occupational studies. These may include:

1. Inadequate job exposure indices specific for women to assess their experience which may differ from men in the same job category.
2. Confounding will result in studies that compare breast cancer incidence and mortality in general population due to breast cancer risk factors such as physical activity, reproductive history, etc. that differ in blue collar jobs, other jobs and those who are not employed.
3. Some studies use mortality as a breast cancer burden indicator that is inadequate given substantial breast cancer survival.
4. Other weaknesses were apparent in studies that had a short follow up period for cancer with a long latency and included women young for breast cancer diagnosis.

5. Misclassification results from errors in modeling, incomplete historical information both for the individual and the setting, and missing or incomplete information regarding behaviors that modify exposure (e.g. use of protective gear at work or amount of time spent outside). Further, similar misclassification errors of women's exposure arise when employment records or death certificates are used rather than more detailed lifetime job histories, because their length of employment in a 'usual' job may be short.
6. Another important methodological problems arise from understating risk due to the healthy worker effect or sensitive workers that leave the job due to short term illness and cancer is not observed. Similarly, using study groups (exposed and control group) from the same polluted region understate the contrast between them.
7. Other difficulties encountered in analysis using large job databases were linking job categories to exposure, interpretation of inconsistencies in jobs with overlapping exposures, comparison of job classification between studies to assume relevant exposure due to correlation between chemical exposures. Also, in well designed studies there were difficulties to assess consistency of found association.

Strength of evidence

Despite a relatively small number of studies, the evidence to date generally supports an association between breast cancer and polycyclic aromatic hydrocarbons (PAHs), in conjunction with certain genetic polymorphisms that lead to suboptimal DNA repair and

thus is involved in carcinogen activation. Evidence also supports an association between polychlorinated biphenyls (PCBs) which are banned, and breast cancer risk in the 10% to 15% of women who carry certain genetic variants. The evidence suggests an association for organic solvents, the evidence is inconclusive for dioxin and finally, the evidence is lacking for organochlorine pesticides.

For dioxin the findings are mixed and the only study that controlled for confounding, reported an increased breast cancer risk for younger women exposed from the Seveso accident. Seveso, Italy, accident is unique and valuable exposure assessment tool because the agent, relative dose, and timing of exposure are likely to be known and to differ markedly from a comparison population. That why continued follow-up with the Seveso cohort is critical.

Lack of evidence for an association between organochlorine pesticides and breast cancer may be due to a true lack of association or to shared methodological weakness across a large number of studies. Because these chemicals are banned in many countries further research should be a priority only when researchers have access to novel data that resolves earlier methodological problems. Also, the exposure to PAHs is widespread and can be reduced, both further study and policies to reduce exposure should be public health priorities.

In summary, there are many chemicals identified in toxicologic research as relevant to breast cancer and they have not been investigated in humans. The development of better exposure assessment methods for epidemiologic research is needed to support evidence from toxicological studies. Job histories and residential histories have the potential to assess exposure at multiple points in time, to integrate exposures across

time, and to integrate exposures to real-world chemical mixtures. The assessment of mixtures, for example, in ambient air, leaves questions concerning which chemical or group of chemicals are responsible for observed effects.(e.g. collapse of the World Trade Center in 2001 and flooding in New Orleans in 2005)

Organic solvents should be a high priority for future breast cancer study. In occupational studies thorough investigation of breast cancer incidence rather than mortality is needed, as well as controlling for confounding by physical activity and other work-related variables.

Also, the conclusions drawn here are limited by factors that affect the identification of relevant research for review and by weaknesses in the underlying studies.

In the meantime, it is advisable to develop national policies to reduce chemical exposures that may be associated with breast cancer. Progress in research on environmental pollutants should encourage strategies to reduce breast cancer risk. Future study also must identify exposures from everyday activities, such as pumping gas, building materials and consumer products. As a good example of relevant exposure from consumer's products is tobacco smoke (PAH) that was found in recent State of California review to be associated with breast cancer in younger women.

4.0 METHODS OF SCREENING

Breast cancer screening is a mode of secondary prevention, a natural extension of primary prevention. Because studies of the etiology of breast cancer have failed to identify feasible primary prevention strategies suitable for use in the general population, reducing mortality from breast cancer through early detection has become a high priority. It is widely accepted that screen-detected cancers have a more favorable prognosis. This may be related to length bias, true benefit of screening, or both in finding cancers at an earlier stage of development. It is also known that screen-detected cancers have favorable cellular characteristics. (Leitch et al, 1977).

The screening methods for breast cancer are numerous. Evaluation of screening methods has generally focused on the performance characteristics of the test, i.e., sensitivity, specificity, and positive predictive value. For example, the specificity of method used is the likelihood of the test being normal when cancer is absent. If specificity is low, many false-positive examinations result in unnecessary follow-up examinations and procedures. The focus today remains on screen- film mammography as a gold standard. Complete information on available screening methods and opinion of Institute of Medicine Report about their effectiveness as a screening tool are summarized in the appendix A.

4.1 Clinical breast exam

Clinical breast examination (CBE) refers to the traditional technique of physical examination of the breast by a health care provider. For average-risk asymptomatic women in their 20s and 30s, it is recommended that CBE be part of a periodic health examination, preferably at least every three years. The exam should include breast self-examination (BSE) instruction for the purpose of gaining familiarity with breast composition.

The examination comprises both systematic inspection and palpation of the nipple, breast, and lymph-draining regions in the axillae, supraclavicular and infraclavicular fossae. (Albert US et al, 2003)

The contribution of the clinical breast examination to early detection is difficult to determine, but studies show that sensitivity is highly dependent on time taken to do the examination. Up to 10 percent of cancers are mammographically silent but evident on clinical breast examination. (Knutson et al, 2007) Screening clinical breast examination detects some cancers missed by mammography, but the sensitivity reported in the community is lower (28% to 36%) than in randomized trials (about 54%).

Weiss et al, 2003 reported that CBE detects about 60% of cancers detected by mammography, as well as some cancers not detected by mammography. There have been no randomized trials comparing breast cancer mortality between women offered and not offered CBE. However, indirect evidence comes from a Canadian study in which women were randomly assigned to CBE alone or CBE plus mammography. Women in the two

groups had similar rates of nodal involvement at diagnosis and of breast cancer mortality. Thus if receipt of mammography averts some deaths from breast cancer, the results of this study suggest that CBE has the potential to do so as well.

Breast self-examination (BSE) has not been shown to be effective in reducing breast cancer mortality, but it does increase the number of breast biopsies performed because of false-positives. (Elmore et al, 2003)

CBE appears to be a promising means of averting some deaths from breast cancer. The examination by itself is inexpensive, as no special equipment is required. It is easy to perform, it can be readily taught to health care providers, and it can be offered ubiquitously. CBE should be part of any program for early detection of breast cancer worldwide, provided that follow-up medical and oncology care is available. (Albert US et al, 2003). Also, it can provide the occasion to raise awareness about breast cancer and to provide accurate education on the variety of breast cancer-related topics.

In a trial that examined the sensitivity and specificity of the test, for 19,965 women aged 50 to 59 years, sensitivity was 83%, 71%, 57%, 83%, and 77% for years 1, 2, 3, 4, and 5 of the trial, respectively, and specificity ranged between 88% and 96%. PPV, which is the proportion of cancers detected per abnormal examination was estimated to be 3% to 4%. For 25,620 women aged 40 to 49 years, who were examined only at entry, the estimated sensitivity was 71%, specificity 84%, and PPV 1.5%. An analysis of 752,081 CBEs performed between 1995 and 1998 as part of the National Breast and Cervical Cancer Early Detection Program found that 6.9% of CBEs were abnormal and that 3.8 invasive cancers and 1.2 cases of DCIS were detected per 1,000 examinations. Sensitivity was 58.8%, specificity 93.4%, and PPV 4.3%. (NIH, 2007)

The USPSTF recommends mammography with or without CBE, and it has concluded that there is insufficient evidence to recommend for or against breast cancer screening with CBE alone. Recommendations for clinical breast examination were modified by adding the advice that women 40 and older schedule annual CBE close to the time of, and before, their annual mammograms. (American Cancer Society Guidelines, 2007)

Published NIH data showed increased sensitivity of mammography-CBE for women aged 60 to 69 years with dense breasts (6.8%), compared with women aged 60 to 69 years with fatty breasts (1.8%). Specificity was lower for women undergoing both (mammography-CBE) screening modalities compared with mammography alone (97% vs. 99%). (NIH, accessed October 8, 2007)

Therefore, after age 40, CBE and BSE are regarded as adjunctive because mammography does not achieve perfect sensitivity. (American Cancer Society Guidelines, 2007)

4.2 Mammography

The U.S. Preventive Services Task Force recommends mammography for women older than 40 years who are in good health, but physicians should consider that sensitivity is lower for younger women. Digital mammography is somewhat more sensitive in younger women and women with dense breasts, studies are currently underway to evaluate the effectiveness of digital mammography in screening of the general population. (Knutson et al, 2007)

Screen-film mammography (SFM) is the current gold standard for breast cancer screening. (American Cancer Society, 2003). Overall sensitivity was approximately 75% but ranges from 54% to 58% in women younger than 40 years to 81% to 94% in those older than 65 years. High breast density is associated 10% to 29% lower sensitivity. (Rosenberg RD et al, 1998). The other factors influencing sensitivity are radiologist's interpretation, already mentioned breast density that is affected by age, endogenous and exogenous hormones, selective estrogen receptor modulators such as tamoxifen, and diet. However, study by Saslow et al, 2007 which proposes guidelines for use of MRI as a screening method, summarized in table A sensitivity and specificity of screening modalities and found sensitivity being lower for mammography than those proposed by Rosenberg. The study included at least 6 prospective, nonrandomized studies from the Netherlands, the United Kingdom, Canada, Germany, the United States, and Italy. There were substantial differences in patient population (age, risk, etc.) and participants in each of these 6 studies had either a documented BRCA1 or BRCA2 mutation or a very strong family history of breast cancer. Some of the studies included women with a prior personal history of breast cancer.

Screening mammography reduces breast cancer mortality by about 20% to 35% in women aged 50 to 69 years and slightly less in women aged 40 to 49 years at 14 years of follow-up. Approximately 95% of women with abnormalities on screening mammograms do not have breast cancer with variability based on such factors as age of the woman and assessment category assigned by the radiologist.

Studies comparing full-field digital mammography to screen film have not shown statistically significant differences in cancer detection while the impact on recall rates (percentage of screening mammograms considered to have positive results) was unclear. A pilot trial from the Centers for Disease Control and Prevention Office of Women's Health has been completed and found sensitivity 75 % with digital mammography and 76% with screen film. Specificity was 79% for both. Computer-aided detection and diagnosis (CAD) systems consist of computer programs that are designed to recognize patterns in images. One study suggested that computer-aided detection increases cancer detection rates and recall rates but decreases specificity, while a second, larger study did not find any significant differences. (Elmore et al, 2005)

4.3 Magnetic resonance imaging (MRI)

Many recently published medical studies have indicated a call for greatly expanded use of magnetic resonance imaging for women who have breast cancer, who are at high risk of developing the disease or who have extremely dense breasts on mammography. Traditional mammography will most likely always remain the premier screening tool for most women. Mammography is very low cost, easy, quick and accurate.

However, MRI is becoming a useful adjunct in breast imaging. Contrast-enhanced breast MRI has demonstrated a high sensitivity approaching 98% generally in the detection of invasive breast cancer. Due to high sensitivity and potential for "too much information," (high false-positive rates) the current guidelines for the use of breast MRI from the American Cancer Society recommend MRI screening in high-risk women 30 years and older who are healthy as an adjunct to screening mammography. High risk is defined as a 20 percent to 25 percent or higher risk of developing breast cancer over the course of a lifetime. The average lifetime risk for women in the United States is 12 percent to 13 percent. (Sweeney et al, 2007)

Other concerns about the potential of MRI as a screening test include costs, the lack of standardized exam techniques and interpretation criteria, the inability of MRI to detect microcalcifications, the ultimate sensitivity of the test, variability of equipment. Systematic review to assess the effectiveness of adding MRI to mammography with or without breast ultrasound and clinical breast examination (CBE) in screening was conducted in study by Lord et al, 2007. Authors found consistent evidence in 5 studies that adding MRI provides a highly sensitive screening strategy (sensitivity range: 93-

100%) compared to mammography alone (25-59%) or mammography plus ultrasound+/- CBE (49-67%).

Meta-analysis of the three studies that compared MRI plus mammography versus mammography alone showed the sensitivity of MRI plus mammography as 94% (95%CI 86-98%) and the incremental sensitivity of MRI as 58% (95%CI 47-70%). Incremental sensitivity of MRI was lower when added to mammography plus ultrasound (44%, 95%CI 27-61%) or to the combination of mammography, ultrasound plus CBE (31-33%). Estimates of screening specificity with MRI were less consistent but suggested a 3-5-fold higher risk of patient recall for investigation of false positive results.

Specificity may range from 37% to 97%. Its low specificity means that special techniques are needed to develop MRI guidance to biopsy performance, as some lesions visible on MRI are not seen by other imaging modalities.

Proposed indications for using MRI for screening include strong family history of breast cancer, patients with BRCA-1 or BRCA-2 oncogene mutations, evaluation of women with breast implants, history of previous lumpectomy or breast biopsy surgeries, axillary metastasis with an unknown primary tumor, very dense or scarred breast tissue (American Cancer Society Guidelines, 2003). No studies assessed as to whether adding MRI reduces patient mortality, interval or advanced breast cancer rates, and did not find strong evidence that MRI leads to the detection of earlier stage disease.

4.4 Ultrasound

Prevalence screening studies in women with radiographically dense breasts have reported three to four breast cancers per 1,000 women that were detected by ultrasound only. In the study done by Saslow et al, 2007 the specificity and sensitivity for ultrasound ranged from 91%-96% and 33%- 40% respectively as shown in Table 2.

An experimental ultrasound technique that measures how easily breast lumps compress and bounce back could enable to determine whether a woman has cancer or not, without having to do a biopsy. In a small study of 80 women, the technique, called "elastography," distinguished harmless lumps from malignant ones with nearly 100 percent accuracy. Cancerous tumors are like stiff springs. Normal tissue and benign lesions compress more easily.

In a clinical trial with Chinese women, UE (ultrasound elastography) was superior to sonography and equal or superior to mammography in differentiating benign and malignant lesions in the breast. A combination of UE and sonography had the best results in detecting cancer and potentially could reduce unnecessary biopsy. (Zhi H et al, 2007)

For lesions of all sizes, ultrasound elastography achieved sensitivity of 80%, specificity of 93%, positive predictive value of 85.3%, and negative predictive value of 90.3%. Sensitivity was best for lesions less than 5 mm (90%), while specificity was best for lesions over 10 mm (95%). For lesions in BI-RADS categories 3 and 4, sensitivity was 68% and specificity was 90%.

Table 2. Assessment of sensitivity and specificity of screening modalities in published breast MRI screening study . (Saslow et al, 2007)

	The Netherlands	Canada	United Kingdom	Germany	US	Italy
No. of centers	6	1	22	1	13	9
No. of women	1,909	236	649	529	390	106
Age range	25-70	25-65	35-49	>30	>25	>25
No. of cancers	50	22	35	43	4	8
Sensitivity(%)						
MRI	89	77	77	91	100	100
Mammogram	33	36	40	33	25	16
Ultrasound	n/a	33	n/a	40	n/a	16
Specificity(%)						
MRI	90	95	81	97	95	99
Mammogram	95	>99	93	97	98	0
Ultrasound	n/a	96	n/a	91	n/a	0

5.0 ROLE OF OCCUPATIONAL MEDICINE IN BREAST CANCER

PREVENTION

Research in the last five years has strengthened the human evidence that not only traditional risk factors for breast cancer need to be considered but that environmental pollutants play a role in breast cancer risk as well. Many of these pollutants can be found in the workplace. Therefore, occupational physicians may be suitable healthcare provider with the opportunity to screen at risk population, female from 18- 65, and influence wide range of presenting risk factors by incorporating prevention into occupational medicine clinic visits.

The examples of two exposures (PAHs and PCBs), for which there is now meaningful evidence of an association with breast cancer, can help us build an evidence-based strategy for preventing breast cancer. Exposure to PAHs is ubiquitous from air pollution, tobacco smoke, and cooked food. The observed relative risks for the PAHs are similar in range to risks typically associated with many well established risk factors for breast cancer, including nulliparity, age at first full-term pregnancy, age at menarche, age at menopause, body weight, hormone replacement therapy, and physical inactivity. Increased risk observed in susceptible women from exposure to PCB's is higher than for many breast cancer risk factors. Because environmental pollutant exposures are both common and avoidable, reducing them should be a public health priority.

5.1 Estimate of population at risk of breast cancer

Total US population is approximately 300 million (304,178,766). Total workforce is currently at 146.3 million. Out of this force approximately 48 % are female according the US census data for 2008. Using US census information allows to stratify US workforce by sex, type of industry (blue and white collar workers) and provide estimate of female population that may be at risk of developing breast cancer as shown in the tables 3 and 4.

Table 3. U.S. female workforce in blue collar jobs.

	blue collar workers	female workers	
		%	number
Agriculture, forestry, fishing and hunting	1958133	20.3	397501
Mining	630321	13	81941.73
Construction	11183930	9.3	10401055
Manufacturing	16350948	29.6	4839880.6
Wholesale trade	4842294	29.7	1438161.3
Retail trade	16268904	49.2	8004300.8
Transportation and warehousing	6006197	25.1	1507555.4
Utilities	1137167	21.7	246765.24
total	58377894		26, 917,161.0

Table 4. U.S. female workforce in white collar jobs.

	white collar workers	Female workers	
		%	number
Information	3524717	43.7	1540301
Finance and insurance, and real estate and rental and leasing	10241270	55.9	5724870
Professional, scientific, and management, and administrative and waste management services:	14301698	43	6149730
Educational services, and health care and social assistance	29491331	74.6	22000533
Arts, entertainment, and recreation, and accommodation and food services	12149998	52.3	6354449
Other services, except public administration	6796996	52.3	3554829
Public administration	6616727	44.4	2937827
total	83122737		48, 262, 539

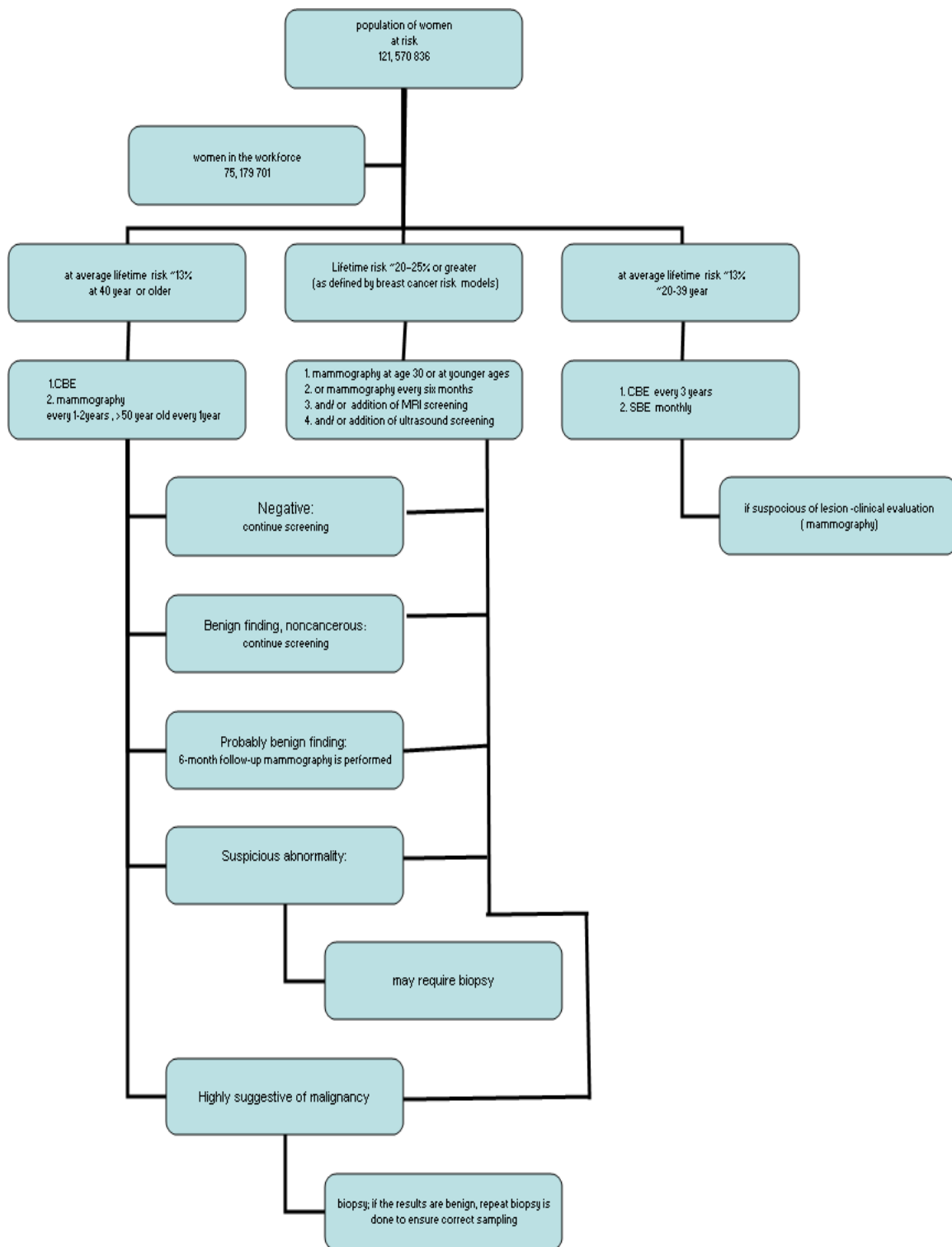


Figure 1. Population at risk of breast cancer in the U.S.

5.2 Workplace screening for breast cancer

Healthy worker effect may preclude many female workers from seeing a physician regularly. Employees have pre-employment physicals, OSHA-mandated physicals, annual physicals, and surveillance exams. The occupational physician can examine these patients and consider breast cancer screening simultaneously. Secondly, using a pre-screening questionnaire focused on personal, demographic and occupational information can help target patients at risk for breast cancer. It is advisable to include occupational information of employment and non-occupational exposures (hobbies) that involved use of organic solvents, polycyclic aromatic hydrocarbons and exposure to polychlorinated biphenyls for which the evidence of association with breast cancer has been meaningful or suggestive. The occupational clinic would be an ideal place to build a tool for registering women with exposures to the above mentioned chemicals. Such as registry for all women followed would help to determine risk estimates with greater accuracy. However, this idea may not be supported and welcomed by majority of employers due to possible costly litigations.

As demonstrated in figure 1, not all women are at the same risk of developing breast cancer. The questionnaire should be further expanded by a tool that estimate risk of breast cancer over the woman lifetime and create a category of high risk women that will benefit from additional and modified screening. Also, cost of screening for these women will be higher than cost for majority of women at average risk (13%). It is estimated that only 1% to 2% of women have a family history suggestive of the

inheritance of an autosomal dominant, high-penetrance gene conferring up to an 80% lifetime risk of breast cancer. Features of the family history which suggest the cancers may be due to such a high-penetrance gene include 2 or more close (generally first- or second-degree) relatives with breast or ovarian cancer; breast cancer occurring before age 50 years (premenopausal) in a close relative; a family history of both breast and ovarian cancer; one or more relatives with 2 cancers (breast and ovarian cancer or 2 independent breast cancers); and male relatives with breast cancer.

The most frequently used models for estimating breast cancer risk are the Gail and Claus Models. The tool allows a health professional to project a woman's individual estimate of breast cancer risk over a 5-year period of time and over her lifetime and compares the woman's risk calculation with the average risk for a woman of the same age.

The Gail Model incorporates a number of established risk factors to estimate a woman's lifetime and 5-year risk for invasive breast cancer. A 5-year risk of 1.7% or higher is considered elevated and meets criteria for certain breast cancer prevention trials. While an excellent assessment tool for most patients, this model is not recommended for use with patients having a strong family history since it excludes some well-established factors associated with hereditary breast cancer. The Gail model is the basis for the Breast Cancer Risk Assessment Tool available Online from the National Cancer Institute.

The Claus Model provides a more accurate estimate of risk for women with a family history of breast cancer by taking into account both maternal and paternal family history, second-degree relatives, and their ages at diagnosis. It also factors within the model a

family history of ovarian cancer. However, unlike the Gail Model, the Claus Model does not include risk factors other than family history.

In addition to these, **The Assessment of Risk Algorithm**, developed by the State of California, Department of Health Services, provides a basic guide for primary care providers to follow and can help identify women at greater risk of breast cancer than the general population. The algorithm attempts to incorporate risk factors that have epidemiologic evidence of significant risk. It does not include all possible risk factors nor does it assess absolute risk for combinations of risk factors. In summary, the algorithm provides a qualitative assessment of risk based on personal history, family history, medical/pathological/genetic factors, with the outcome of either normal or increased risk for breast cancer. (Cancer screening and diagnosing, accessed May 20, 2008)

Based on expert consensus opinion if the lifetime risk is approximately 20-25% identified by these or other models then addition of annual MRI screening is recommended (figure 1), insufficient evidence exist for lifetime risk of 15-20% and consensus is against MRI use is the lifetime risk is at 15%.

Other risk factors for breast cancer have been identified or proposed but are not included for several reasons: because evidence that these factors contribute to breast cancer risk is not conclusive, because researchers cannot determine whether these factors add useful information to factors already in the model, or because data on other risk factors was not available in the research data used to develop the model. Such risk factors include: age at menopause, use of birth control pills, high body mass index, a high-fat diet, alcohol, radiation exposure, and environmental pollutants. Recently published research indicates that breast tissue density can add useful information, but risk models

with breast tissue density measurement still need to be validated with additional independent studies. Research also indicates that other risk factors, such as use of hormone therapy, might improve the tool (NCI, 2008).

5.3 Cost- effectiveness of screening

Employers, particularly large corporations and agencies, must realize that by introducing effective work site cancer screening programs they not only fulfill their social responsibility to contribute to their employee's health, but also achieve reductions in health care costs, as well as costs associated with ill worker replacement. Chronic diseases such as cancer are having a negative impact on employee productivity and unhealthy individuals cost more to insure. Thus to keep employees healthy will keep them in the low cost insurance group. (Oregon.gov, 2007). Employers can offer periodic screening as an employee health benefit, and/or establish screening programs in the workplace that consist of CBE in combination with other modalities of which mammography is best established.

To draw a scenario of such a screening effectiveness, one should consider the number of female workers in the US workforce - approximately 75 million (figure 1). Only about 2 mammograms out of every 1,000 or 0.2%, lead to a diagnosis of breast cancer. Hypothetically, if all women in the US workforce have been screened, it would identified about 150, 000 women in the early stage of breast cancer that is more responsive to the most current and improved breast cancer therapy and that prolongs survival time and saves lives. It may also result in economic savings if early-stage cancer is less expensive to treat Screen-film mammography (SFM) is the current gold standard for breast cancer screening. (American Cancer Society, 2003). The mean total cost per woman can be estimated as \$124 according published study by Poplack et al, 2005 of which \$99 was attributable to imaging, and \$25 to consultation and/or intervention. The

cost of screening of the above mentioned cohort would come to a number of \$9,3 billion. The mean cost of treatment of breast cancer that includes breast conservation therapy (BCT), radiation therapy, adjuvant therapy was at 5 years after diagnosis \$32, 246. (Barlow et al, 2001). To treat the 0.2% of cohort for breast cancer has been estimated to \$4, 836 900 000. If estimating a value of a life saved to 6 million in the US dollars, rough estimate of saved lives by mammography screening (~ 30% of mortality reduction) would be \$270 billion. Total cost of screening and breast cancer treatment of US female workforce then will be \$14, 136 900 000 with estimation of savings of those who will be successfully treated \$256 billion.

Employer-sponsored breast cancer screening programs can be provided in the following settings: on-site within an employer, mobile unit visiting the employer, and off-site. Off site visits can be an attractive option for employers that already offer health plan benefits to employees that covers expenses incurred by mammography screening. Providing a time for women to visit screening facility would serve a public health cause to reduce breast cancer mortality. Appendix A provides information on US states mammography coverage laws in table 6.

In study by Kessler et al, 1991 mobile screening mammography was offered to 3,627 employees of a large corporation in Pennsylvania and Delaware. Women were charged \$30 for a standard two-view examination. They also received health education materials on mammography and breast self-examination. The remaining costs of the program were underwritten by the corporation. During this program, 3,627 mammographic studies were performed; 63 biopsies were recommended. 57 biopsies were performed, and 9 cancers were diagnosed. The authors concluded that mobile

screening programs at the work site was inexpensive, convenient alternative to more traditional screening programs. The advantages of this program were the low cost, the relative ease with which the examination can be performed, and the positive role that corporate medical personnel assume in encouraging individual and group participation.

Workplace screening with mobile mammography is one possible approach to the convenience barrier. However, fixed-facility workplace screening is a viable alternative for any company with a large workforce in one location. (Reynolds HE et al, 1997)

The cost of mammography itself and of diagnostic work-up are two of the largest costs involved (table 5). Therefore, the most efficient approach to providing mammography depends on the number of employees receiving mammography; and the diagnostic accuracy of mammography and underlying incidence of breast cancer in screened population. Especially in population of working women with identifiable risk factors, screening is cost-effective because the expenditure required to save a year of life through early detection of breast cancer is low compared to other types of health services for which employers commonly pay. (Griffiths RI et al, 1998)

Study by Schrammel P et al, 1999 evaluating on - site workplace screening is a relatively efficient approach for early detection of breast cancer when compared to off site screening or no screening. This study was performed to identify the employer costs of breast cancer screening in the workplace, referrals for suspicious findings, and initial treatment of malignant disease. Additionally, the costs for these same services, had they been obtained outside of a workplace screening program, were estimated. These costs were compared to those among a hypothetical cohort of women not enrolled in the workplace screening program. 1,416 women participated in the program. Nearly 2,500

screening mammograms and approximately 2,773 clinical breast examinations were performed, resulting in 292 referrals to physicians outside of the program for additional diagnostic procedures and treatment as needed. Mammographic and clinical breast examination screening cost \$249,041; (table 5) referrals resulting in benign disease or no detectable disease cost \$185,002; and referrals resulting in malignant disease, followed by initial treatment, cost \$148,530. Therefore, the total cost was \$582,573. Approximately 47% of the cost of referrals and initial treatment were due to employee lost productivity. Total cost in the hypothetical cohort was \$1,067,948 under the assumptions that all women received screening outside of the workplace, and that the same number of malignancies were detected at the same stage as in the workplace program.

Table 5. CPT Service Codes and Corresponding National Medicare Global Allowable Reimbursement Amounts for 2002

Service	CPT code	National Medicare Global Charge(\$)
Bilateral screening mammography	76092	81.81
Unilateral diagnostic mammography	76090	73.48
Bilateral diagnostic mammography	78091	90.5
US	76645	65.52
US-guided biopsy	76942	89.05
Stereotactic biopsy	76095	338.46
Needle placement	19290	64.43
Clinical breast examination	99212	23.17
Surgical consultation	99242	68.05
Breast biopsy, percutaneous, core-needle	19102	102.81
Breast biopsy, percutaneous, automated vacuum-assisted or rotating biopsy device	19103	187.15
Mammographic guidance for needle placement	76096	75.66

5.4 Summary

Screening for breast cancer can result in early detection of malignancies and lives saved. The progress has been made in the US in expanding life-saving access to breast cancer screening and treatment but not in substantially reducing incidence. Many of the identified risk factors, including family history, age at menarche and menopause, parity, breast density, and age at a first full-term pregnancy, cannot be readily modified. Pursuing new evidence of risk factors that can be changed is a crucial priority if we are to achieve a world without breast cancer. (Devra Lee Davis et al, 2003)

The worksite can be a suitable place for both – prevention (screening) and assessment of cancer risk as outlined previously. This review supports screening by occupational medicine physicians for breast cancer (detection of suspicious lesions) and making an appropriate referral. Occupational medicine physicians have the opportunity to detect a breast cancer in a population that may not routinely see a physician and may be in higher risk than general population. Focusing a few minutes of the examination on breast cancer screening may prevent patient morbidity and mortality.

Study by Schrammel P et al, 1999 showed that workplace screening is a relatively efficient approach for early detection of breast cancer .The efficiency could be improved with a reduction in the number and cost of unnecessary referrals. That place an emphasis on occupational medicine physician to improve his or her breast cancer detection knowledge if they were to begin breast cancer screening examinations.

To improve skills of occupational medicine physicians in clinical and counseling skills (screening mammography) the workshops utilizing standardized patients could be a choice. The overall clinical breast exam score increased substantially from 24.8 to 34.7 ($P < 0.0001$) in study done by Costanza et al, 1999. The basic course cost \$202 per physician trained.

With increased emphasis placed on breast cancer screening by ACOEM in cooperation with other breast cancer organizations, it is likely that awareness of breast cancer will be raised in the workplace. With education and continued efforts there is a hope that management of large corporations will support comprehensive breast cancer screening, thus fulfill their social responsibility to contribute to their employee's health.

APPENDIX: TABLE 6 and TABLE 7

TABLE 6. Potential New Imaging Technologies for Breast Cancer Detection*

Technology	Current Level of Evidence Supporting Use in Screening	FDA Approval for General Clinical Use	FDA Approval Specifically for Screening
Screen-film mammography (SFM)	A	Yes	Yes
Full-field digital mammography (FFDM)	B	Yes	Yes
Computer-aided detection with SFM	B	Yes	Yes
Computer-aided detection with FFDM	B	Yes	Yes
Ultrasound (US)	B	Yes	No
Magnetic resonance imaging (MRI)	B	Yes	No
Novel ultrasound methods (Doppler, 3D, compound scanning, etc.)	C	No	No
Computer-aided detection with US	C	No	No
Computer-aided detection with	C	No	No

Table 6 continued

MRI			
X-ray computer tomography (CT)	C	Yes	No
Scintimammography	C	Yes	No
Positron emission tomography (PET)	C	Yes	No
Elastography (MR and US)	C	No	No
Magnetic resonance spectroscopy	C	No	No
Optical imaging	C	No	No
Optical spectroscopy	C	No	No
Electrical potential measurements	C	No	No
Electrical impedance imaging	C	Yes	No
Electronic palpation	C	No	No
Dedicated breast CT (x-ray, US, optical, thermoacoustic)	C	No	No
Thermography	D	Yes	No

Table 6 continued

Magnetomammography	E	No	No
Microwave imaging	E	No	No
Hall effect imaging	E	No	No
<p>Key:</p> <p>A = Strong clinical evidence for effectiveness in screening; technology is routinely used for screening.</p> <p>B = Some clinical evidence for effectiveness or equivalence to screen-film mammography for screening.</p> <p>C = Preclinical data suggest possible promise, but clinical data are sparse or nonexistent; more study is needed.</p> <p>D = Clinical evidence indicates that modality is ineffective as a screening tool.</p> <p>E = Technology is not at the stage that data are available.</p> <p>*Adapted with additions and minor changes from Table 2-1, Institute of Medicine Report on New Technologies in Breast Imaging, 2001</p>			

TABLE 7. States with Mammography Screening Coverage Laws

State	Code	Frequency and Age Requirements
AK	1	baseline for ages 35-39, every two years for 40s, each year 50+, or physician rec.
AL	6	every two years for 40s or physician rec.; each year for 50+ or physician rec.
AR	1	Insurers must <u>offer</u> baseline for ages 35-39, every two years for 40s, each year 50+, or physician rec.
AZ	1	baseline for ages 35-39, every two years for 40s, each year 50+, or physician rec.
CA	1	baseline for ages 35-39, every two years for 40s, each year 50+, or physician rec.
CO	1	baseline for ages 35-39, every two years for 40s, each year 50+, or physician rec.
CT	1	baseline for ages 35-39, every two years for 40s, each year 50+, or physician rec.
DC	5	coverage
DE	1	baseline for ages 35-39, every two years for 40s, each year 50+
FL	1	baseline for ages 35-39, every two years for 40s, each year 50+, or physician rec.
GA	1	baseline for ages 35-39, every two years for 40s, each year 50+, or physician rec.
HI	5	annual for 40+, or physician rec.
IA	1	baseline for ages 35-39, every two years for 40s, each year 50+, or physician rec.
ID	1	baseline for ages 35-39, every two years for 40s, each year 50+, or physician rec.
IL	5	baseline for ages 35-39, annual for 40+
IN	5	annual for 40+, or physician rec.
KS	4	Covered in accordance with American Cancer Society guidelines when reimbursement is provided for lab and X-ray services
KY	1	baseline for ages 35-39, every two years for 40s, each year 50+
LA	1	baseline for ages 35-39, every two years for 40s, each year 50+, or physician rec.
MA	5	baseline for ages 35-39 and annual for 40+

Table 7 continued

MD	1	baseline for ages 35-39, every two years for 40s, each year 50+, or physician rec.
ME	5	annual for 40+
MI	5	Insurance must <u>offer</u> baseline for ages 35-39, annual for 40+
MN	4	if recommended
MO	1	baseline for ages 35-39, every two years for 40s, each year 50+, or physician rec.
MS	other	Insurance must <u>offer</u> annual for ages 35+
MT	1	baseline for ages 35-39, every two years for 40s, each year 50+, or physician rec.
NC	1	baseline for ages 35-39, every two years for 40s, each year 50+, or physician rec.
ND	5	baseline for ages 35-39, annual for 40+, or physician rec.
NE	1	baseline for ages 35-39, every two years for 40s, each year 50+, or physician rec.
NH	1	baseline for ages 35-39, every two years for 40s, each year 50+
NJ	5	baseline for ages 35-39, every two years for 40s, each year 50+, or physician rec.
NM	1	baseline for ages 35-39, every two years for 40s, each year 50+, or physician rec.
NV	5	baseline for ages 35-39 and annual for 40+
NY	1	baseline for ages 35-39, every two years for 40s, each year 50+, or physician rec.
OH	1	Insurance must <u>offer</u> baseline for ages 35-39, every two years for 40s, one if a woman is at least 50 but under 65, or physician rec.
OK	5	baseline for ages 35-39 and annual for 40+
OR	5	Annual for 40+, or by referral
PA	other	annual for 40+, physician rec for under 40
RI	other	according to ACS guidelines
SC	other	baseline for ages 35-39, every two years for 40s, each year 50+, or physician rec., in accordance with American Cancer Society guidelines
SD	1	baseline for ages 35-39, every two years for 40s, each year 50+, or physician rec.
TN	1	baseline for ages 35-39, every two years for 40s, each year 50+, or physician rec.
TX	other	annual for 35+

Table 7 continued

UT	N/A	none
VA	1	baseline for ages 35-39, every two years for 40s, each year 50+
VT	other	annual for 50+, physician rec for under 50
WA	4	if recommended
WI	other	two exams total for ages 45-49, each year 50+
WV	1	baseline for ages 35-39, every two years for 40s
WY	N/A	none

Legend:

1 baseline for ages 35-39, every two years for 40s, each year 50+, or physician rec.

3 baseline for ages 35-39, every 1-2 years for 40s, each year 50+

4 if recommended

5 baseline for ages 35-39 and annual for 40+

6 every two years for 40s, each years for 50+

Chart Source: National Conference of State Legislatures, Health Policy Tracking Service, 10/02/00

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